Request for Information (RFI): Production of 7.5 Grams of Clinical Grade Plasmid DNA
6/20/2013

Notice Number:

RFI13-152

Key Dates:

Release Date: June 20, 2013

Responses Due: Responses will be accepted as long as this RFI is posted

Related Announcements:

None

Issued By:

SAIC-Frederick, Inc.
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Overview

The Frederick National Laboratory for Cancer Research (FNLCR, http://ncifrederick.cancer.gov/) a national laboratory operated by SAIC-Frederic under a contract from the National Cancer Institute (NCI) is seeking information to gain feedback, comments, and novel ideas for cGMP manufacturing of plasmid DNA at gram scale. The Biopharmaceutical Development Program (BDP) developed the technology and has successfully delivered five products for clinical trials in the past. The manufacturing process consists of master cell bank preparation, bacterial fermentation, recovery and purification, and formulation and filling. The product is tested for identity, content, activity, purity and safety before released for clinical trials. The product is usually stored frozen and stable for years.

With the existing manufacturing process in BDP, it requires 100L of fermentation broth to produce 1 gram of final product. The lysis, recovery and downstream purification process can be linearly scaled up to meet the deliverable requirements. The scale-up will be confirmed at pilot scale.

Preliminary in-house development studies indicate the fermentation can be improved to significantly increase the volumetric yield of plasmid up to 5 fold. The technology is to be further developed for GMP production.

Information Requested
(with the assumption that a GMP master cell bank is available. See table 1.0 Plasmid DNA Production Process Outlines for details)

Please provide detailed information as to how the existing process can be scaled up

- Pilot run at 150L fermentation scale

- GMP run at 500L fermentation scale (2 fermentation runs)
- Testing and release
- Regulatory affairs

Please provide detailed information as to how the existing process can be scaled up with improved Fermentation

- Development at 30L fermentation scale
- Pilot run at 150L fermentation scale
- GMP run at 500L fermentation scale (1 fermentation run)
- Testing and release
- Regulatory affairs

If you choose to use your own production process to achieve the goal of making 7.5 grams of clinical grade plasmid, please provide detailed information on your process.

Table 1.0 Plasmid DNA Production Process Outlines

Process	BDP Existing Process	Scaled Up Process	Scaled Up Process with improved Fermentation (5x cell mass increase)
Deliverable	1.3 g	7.5 g	7.5 g
Fermentation	2x 80L w/ 65 L working volume	500 L w/ 400 L working volume; 1 pilot run at 150L scale, 1 engineering run plus 2 GMP runs at 500L scale	500 L w/ 400 L working volume; 3 development runs at 30L scale, 1 pilot run at 150 L scale, 1 engineering run plus 1 GMP run at 500L scale
Lysis	150L after lysis and neutralization	1x pilot run at 150L scale; 2x 450L GMP runs	3 development run at 50L scale, 1x pilot run at 150L scale; 2x450L GMP runs
Recovery and purification	Two column steps with alcohol precipitation and UF/DF	Two column steps with alcohol precipitation and UF/DF	Two column steps with alcohol precipitation and UF/DF

Table 1.1 Plasmid DNA Assay Profiles

Drug Substance	**Drug Product**
IDENTITY • Restriction Mapping	IDENTITY • Appearance • DNA Sequence • Restriction Mapping
CONTENT • DNA Concentration by absorbance at 260 nm	CONTENT • DNA Concentration by absorbance at 260 nm
ACTIVITY • Detection of protein expression by Western Blot following plasmid transfection of mammalian cells	ACTIVITY • Detection of protein expression by Western Blot following plasmid transfection of mammalian cells
PURITY • DNA purity A260nm / A280nm Ratio • % Supercoiled Plasmid DNA by IEX-HPLC • Residual RNA • Residual E. coli Genomic DNA • Residual Isopropanol • Residual Ethanol • Residual Protein	PURITY • DNA Purity A260nm / A280nm Ratio • % Supercoiled Plasmid DNA by IEX-HPLC

SAFETY • Endotoxin (LAL) • Bulk Sterility • Bacteriostasis / Fungistasis	SAFETY • Endotoxin (LAL) • pH • Sterility • Rabbit Pyrogen

Note: Do not include any proprietary information

If you are willing to do so, please indicate your primary affiliation/role from the categories listed below:

- Academia (basic or clinical research)
- Small Business
- Pharmaceutical/Biotechnology Industry
- Federal Government
- State Government
- Healthcare Professional organization
- Integrative Medicine Professional organization;
- Patient Advocacy Group;
- Country; and
- Other (briefly define).

How to submit a response

Please submit detailed and concise responses.

Responses should be returned to:
Calvin Proffitt
Manager, Subcontracts
proffittch@mail.nih.gov

Attached Documents (Microsoft Word.doc or Adobe Acrobat.pdf files)

Inquiries

Inquiries regarding this RFI should be directed to:
Calvin Proffitt
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